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Sub therapeutic rivaroxaban plasma concentrations following administration via Percutaneous Endoscopic Gastrostomy (PEG) feeding tubes – a note of caution

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Rivaroxaban is a direct factor Xa inhibitor currently licensed for the acute treatment and prevention of venous thromboembolism and for the prevention of stroke in the context of atrial fibrillation (AF). Rivaroxaban is rapidly absorbed with maximum concentrations reported around 2 - 4 hours post ingestion. Oral bioavailability is high (80 - 100%) for the 2.5mg and 10 mg tablet dose under fasting conditions or with food. The 20mg dose of rivaroxaban has reduced bioavailability of 66%, under fasting conditions, increasing to near 100% when taken with food [SPC, 2016]. Absorption of rivaroxaban is dependent on the site of its release in the gastrointestinal tract. A 29% and 56% decrease in area-under the concentration-time-curve (AUC) and Cmax compared to tablet is reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when rivaroxaban is released in the distal small intestine, or ascending colon [SPC, 2016]. Therefore, administration of rivaroxaban distal to the stomach should be avoided since this can result in reduced absorption and related rivaroxaban exposure. For patients unable to ingest whole tablets, rivaroxaban may be given through a gastric tube after confirmation of the correct placement of the tube. It is suggested that the crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water. The dose of rivaroxaban should then be immediately followed by enteral feeding [Moore *et al*., 2014; SPC, 2016].

We report our experience of administering rivaroxaban via a PEG tube in three patients requiring oral anticoagulation therapy, following a cardioembolic stroke (table 1). A direct oral anticoagulant was selected over warfarin in order to reduce the need for regular INR testing in the community and as part of a local initiative to decrease district nursing workload.

Table 1: Details of the 3 cases who had rivaroxaban administered via a PEG tube, for the secondary prevention of stroke in the context of AF

	Case 1	***Case 2***	***Case 3***
Gender	M	M	M
Age	78	85	82
CHA_2DS_2Vasc score	5	5	5
Stroke	Left vertebral artery occlusion	left centrum semiovale infarct	Left middle cerebral artery infarct
Dose	20mg daily	20mg daily	20mg daily
CrCL (mL/min)*	103	42	62
Timing of feed	PEG feed given 12am to 5pm, rivaroxaban given 8.50am (1st level) PEG feed given 1.30pm-9.30am, rivaroxaban given 8.50pm (2nd level)	Bolus PEG feed regime with Fortisip at 8am, 1pm and 6pm and Calogen at 3pm Rivaroxaban given at 6pm	PEG feed given 12am to 2pm Rivaroxaban given at 1.40pm
Rivaroxaban plasma concentration (ng/ml)**	<20 (14 hours post dose) 61 (3 hours post dose)	64 (3 hours post dose)	76 (3.5 hours post dose)
Number of doses of rivaroxaban recieved prior to level	14	8	2
Outcome	Switched to warfarin	Switched to apixaban and transferred to local hospital for rehabilitation	Switched to apixaban with an adequate trough concentration achieved (65 ng/ml)

**calculated using Cockcroft - Gault equation*

*** STA-liquid anti-Xa assay® (Diagnostica Stago, France), with appropriate rivaroxaban calibrators and controls*

Following ingestion of rivaroxaban, the mean plasma concentrations for the 20mg dose or rivaroxaban in the AF population at 3 hours is reported to be 246 ng/mL (5^{th}-95^{th} percentile: 172–361) [Mueck *et al*., 2013]. As can be seen from table 1, the concentrations achieved by these patients are significantly lower than what one might expect.

The administration of rivaroxaban via gastric tubes is recommended by the manufacturers of the agent, based on work in 55 healthy adults, by Moore and colleagues [2014]. This study reports that when rivaroxaban is crushed and administered via a NG tube, a similar relative bioavailability

compared to a whole tablet ingested is achieved. However, a report from Japan, where licensed doses of rivaroxaban are lower than those recommended elsewhere world-wide, reports that Japanese stroke patients receiving crushed rivaroxaban tablets had significantly lower rivaroxaban concentrations, than those stroke patients receiving the whole tablets at the equivalent dose [Okata *et al*., 2014].

When tablets are crushed, there is always the possibility that some may be lost in the crushing device, adsorbed to the feeding tube and lost in its transfer from the crushing device to the feeding tube. Furthermore, rivaroxaban has poor water solubility and does not easily suspend in water, therefore making a suitable liquid preparation on the ward environment would be challenging. Our limited experience and that from Japan does suggests that significantly lower rivaroxaban concentrations are observed, when tablets are crushed and administered by a feeding tube in clinical practice and it would be sensible to assay rivaroxaban plasma concentrations when used in scenarios like this.

Other direct oral anticoagulants, whose absorption is not dependent on food, may result in adequate plasma concentrations. . Indeed apixaban's absorption is not dependent on food and apixaban's manufacturers suggest that following administration of a crushed 5 mg apixaban tablet suspended in 60 mL of water and delivered via a nasogastric tube, exposure is similar to exposure seen in clinical trials involving healthy subjects receiving a single oral 5 mg apixaban tablet dose [SPC, 2016]. Switching from rivaroxaban to apixaban was the course of action taken in 2 of the 3 cases presented here, with an apixaban plasma concentration being measured in 1 patient and found to be adequate. Edoxaban has also shown similar exposure to that seen in healthy subjects receiving a single 60mg dose, when crushed, mixed with water and administered via a nasogastric tube [Duchin et al 2017]. Dabigatran cannot be administered via gastric tubes due to the significantly increased bioavailability of dabigatran if it is administered without the capsule shell. [SPC, 2018].

In conclusion, if rivaroxaban is administered via a gastric tube, it would be prudent to measure plasma concentrations to ensure adequate exposure is being achieved. It may be possible to achieve adequate rivaroxaban plasma concentrations when administered via gastric tube providing the rivaroxaban SPC instructions are followed to the letter. As our experience has shown this may be difficult to achieve in clinical practice. If adequate DOAC concentrations are not achieved through

crushing process, then a vitamin K antagonist like warfarin with INR monitoring does remain a suitable option.

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Conflicts of Interests

The authors have no relevant conflicts of interest to declare.